IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

TRIS PHARMA, INC., Plaintiff,	)	
v.	)	C.A. No. 14-1309-GMS CONSOLIDATED
ACTAVIS LABORATORIES FL, INC., Defendant.	)	

MEMORANDUM

I. INTRODUCTION

In this Hatch-Waxman patent infringement action, plaintiff Tris Pharma, Inc. ("Tris") alleges patent infringement by defendant Actavis Laboratories FL, Inc. ("Actavis"). Plaintiff alleges that, by filing Abbreviated New Drug Applications ("ANDAs") seeking approval to market generic versions of Quillivant XR®, Defendant infringed U.S. Patent Nos. 8,46,765 ("the '765 patent"), 8,563,033 ("the '033 patent"), 8,778,390 ("the '390 patent"), 8,956,649 ("the '649 patent"), 9,040,083 ("the '083 patent"). The court held a five-day bench trial in this matter beginning on February 6, 2017. Presently before the court are the parties' post-trial proposed findings of fact and conclusions of law concerning infringement of and the validity of the patents-in-suit, specifically whether the asserted claims are invalid as obvious under 35 U.S.C. § 103. (D.I. 151; D.I. 152.)

Pursuant to Federal Rule of Civil Procedure 52(a), having considered the entire record in this case and the applicable law, the court concludes that all asserted claims of the patents-in-suit are invalid due to obviousness. These findings of fact and conclusions of law are set forth in further detail below.

II. FINDINGS OF FACT[1]

A. The Parties

1. Plaintiff Tris Pharma, Inc. is a company organized and existing under the laws of New Jersey, having its principal place of business at 2033 Route 130, Suite D, Monmouth Junction, NJ 08852.

2. Defendant Actavis Laboratories FL, Inc. is a corporation organized and existing under the laws of Florida, having an address at 2945 W. Corporate Lakes Blvd., Weston, FL.

3. The court has subject matter jurisdiction and personal jurisdiction over all parties.

B. Background

4. Tris holds an approved New Drug Application ("NDA") No. 202100 under Section 505(a) of the Federal Food, Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. § 355(a), for an extended release methylphenidate suspension, which Tris sells under the trade name Quillivant XR®.

5. On September 27, 2012, the United States Food and Drug Administration ("FDA") approved Quillivant XR® for treatment of Attention Deficit Hyperactivity Disorder (ADHD).

6. Pursuant to 21 U.S.C. § 355(b)(1), and attendant FDA regulations, the '667 Patent, the '903 patent, the '765 patent, the '033 patent, the '390 patent, the '649 patent, and the '083 patent (collectively, "the patents-in-suit") are listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to Quillivant XR®.

C. The Patents-in-Suit

7. The '765 patent issued on June 18, 2013 and is entitled "Orally Effective Methylphenidate Extended Release Powder And Aqueous Suspension Product." The '765 patent names Ketan Mehta, Yu-Hsing Tu, and Ashok Perumal as inventors. Tris Pharma, Inc. is the assignee of the '765 patent.

8. The '033 patent issued on October 22, 2013 and is entitled "Orally Effective Methylphenidate Extended Release Powder And Aqueous Suspension Product." The '033 patent names Ketan, Mehta, Yu-Hsing Tu, and Ashok Perumal as inventors. Tris Pharma, Inc. is the assignee of the '033 patent.

---

[1] Prior to trial, the parties submitted an exhibit of uncontested facts in conjunction with their Pretrial Order. (D.I. 141, Ex. 1.) The court takes most of its findings of fact from the parties' uncontested facts. The court has also reordered and renumbered some paragraphs and made minor edits for the purpose of concision and clarity that it does not believe alters the meaning of the paragraphs from the Pretrial Order. Otherwise, any differences between this section and the parties' statement of uncontested facts are unintentional.

The court's findings of fact with respect to matters that were the subject of dispute between the parties are included in Part III this opinion ("Discussion and Conclusions of Law"), preceded by the phrase "the court finds" or "the court concludes."

9. The '390 patent issued on July 15, 2014 and is entitled "Orally Effective Methylphenidate Extended Release Powder And Aqueous Suspension Product." The '390 Patent names Ketan Mehta, Yu-Hsing Tu, and Ashok Perumal as inventors. Tris Pharma, Inc. is the assignee of the '390 patent.

10. The '649 patent issued on February 17, 2015 and is entitled "Orally Effective Methylphenidate Extended Release Powder And Aqueous Suspension Product." The '649 patent names Ketan Mehta, Yu-Hsing Tu, and Ashok Perumal as inventors. Tris Pharma, Inc. is the assignee of the '649 patent.

11. The '083 patent issued on May 26, 2015 and is entitled "Orally Effective Methylphenidate Extended Release Powder And Aqueous Suspension Product." The '083 patent names Ketan Mehta, Yu-Hsing Tu, and Ashok Perumal as inventors. Tris Pharma, Inc. is the assignee of the '083 patent.

(1) The Asserted Claims

12. Tris has asserted infringement of claims 6, 13, 16, 18, 20, 25, and 30 of the '765 patent against Actavis.

13. Tris has asserted infringement of claims 4 and 10 of the '033 patent against Actavis.

14. Tris has asserted infringement of claims 15, 16, and 20 of the '390 patent against Actavis.

15. Tris has asserted infringement of claims 12, 22, 23, 25, 26, 27, and 33 of the '649 patent against Actavis.

16. Tris has asserted infringement of claims 5, 6, 7, 8, 12, 15, 16, and 17 of the '083 patent against Actavis.

i. '765 Patent, Claim 6

17. Claim 6 of the '765 patent reads:

> The suspensions according to claim 1, wherein the suspension has a pharmacokinetic profile in which the single mean plasma concentration peak for d-methylphenidate has an area under the curve (AUC)0-∞ of about 114 ng-hr/mL to about 180 ng-hr/mL, C_{max} of about 11 ng/mL to about 17 ng/mL, T_{max} of about 4 hours to about 5.25 hours and T1/2 of about 5 hours to about 7 hours following a single oral administration of an aqueous suspension at a dose equivalent to 60 mg racemic methylphenidate HCL in adults.

ii. '765 Patent, Claim 13

18. Claim 13 of the '765 patent reads:

The suspension according to claim 1, wherein said suspension contains at least about 80% of water by weight based on the total weight of the suspension.

iii. '765 Patent, Claim 16

19. Claim 16 of the '765 patent reads:

The suspension according to claim 1, wherein the suspension contains about 10 to about 30 parts by weight of methylphenidate as provided in the immediate release component and to about 70 to about 90 parts by weight of sustained release methylphenidate, based upon the total weight of methylphenidate in suspension.

iv. '765 Patent, Claim 18

20. Claim 18 of the '765 patent reads:

The suspension according to claim 17, wherein the buffering agent is a mixture of sodium citrate and anhydrous citric acid.

v. '765 Patent, Claim 20

21. Claim 20 of the '765 patent reads:

The method according to claim 19, wherein the suspension which has a pH from about 4 to about 4.5.

vi. '765 Patent, Claim 25

22. Claim 25 of the '765 patent reads:

The powder blend according to claim 23, wherein the surfactant in the diluent granules comprises a poloxamer.

vii. '765 Patent, Claim 30

23. Claim 30 of the '765 patent reads:

The methylphenidate aqueous extended release oral suspension according to claim 29, which has less than about 3% loss in potency over a period of at least 4 months of storage at room temperature.

viii. '033 Patent, Claim 4

24. Claim 4 of the '033 patent reads:

The suspension according to claim 1, wherein said suspension contains at least 80% of water by weight based on the total weight of the suspension.

ix. '033 Patent, Claim 10

25. Claim 10 of the '033 patent reads:

The method according to claim 9, wherein the suspension which has a pH from about 4 to about 4.5.

x. '390 Patent, Claim 15

26. Claim 15 of the '390 patent reads:

The suspension according to claim 14 which comprises about 10 to 30 parts by weight of methylphenidate as provided in the immediate release component and to about 70 to about 90 parts by weight of methylphenidate as provided in the sustained release component, based upon the total weight of methylphenidate in suspension.

xi. '390 Patent, Claim 16

27. Claim 16 of the '390 patent reads:

The suspension according to claim 1, wherein said suspension contains at least 80% of water by weight based on the total weight of the suspension.

xii. '390 Patent, Claim 20

28. Claim 20 of the '390 patent reads:

The suspension according to claim 3, wherein the suspension has less than about 5% loss in potency over a period of at least about 4 months at room temperature.

xiii. '649 Patent, Claim 12

29. Claim 12 of the '649 patent reads:

The methylphenidate aqueous extended release oral suspension according to claim 11, wherein the hydrophilic polymer is polyvinylpyrrolidone.

xiv. '649 Patent, Claim 22

30. Claim 22 of the '649 patent reads:

The methylphenidate aqueous extended release oral suspension according to claim 19, which has less than about 5% loss in potency over a period of about 4 months of storage at room temperature.

xv. '649 Patent, Claim 23

31. Claim 23 of the '649 patent reads:

The methylphenidate aqueous extended release oral suspension according to claim 19, which has less than about 1% of threo-α-phenyl-2-piperidineacetic acid hydrochloride impurity after a period of about 4 months of storage at room temperature.

xvi. '649 Patent, Claim 25

32. Claim 25 of the '649 patent reads:

The methylphenidate aqueous extended release oral suspension according to claim 17, wherein said suspension provides a therapeutically effective plasma profile for methylphenidate for about 12 hours following a single oral administration of an aqueous suspension at a dose equivalent to 60 mg racemic methylphenidate HCl in adults.

xvii. '649 Patent, Claim 26

33. Claim 26 of the '649 patent reads:

The methylphenidate aqueous extended release oral suspension according to claim 17, wherein said suspension provides a single mean average plasma concentration peak for methylphenidate following a single oral administration of an aqueous suspension at a dose equivalent to 60 mg racemic methylphenidate HCl in adults.

xviii. '649 Patent, Claim 27

34. Claim 27 of the '649 patent reads:

The methylphenidate aqueous extended release oral suspension according to claim 17, wherein said suspension provides a therapeutically effective amount of methylphenidate within 45 minutes after administration following a single oral administration of an aqueous suspension at a dose equivalent to 60 mg racemic methylphenidate HCl in adults.

xix. '649 Patent, Claim 33

35. Claim 33 of the '649 patent reads:

The methylphenidate aqueous extended release oral suspension according to claim 17, wherein the barrier coating comprises ethycellulose.

xx. '083 Patent, Claim 5

36. Claim 5 of the '083 patent reads:

The powder according to claim 2, wherein the suspension has less than about 5% loss in potency over a period of about 4 months of storage at room temperature.

xxi. '083 Patent, Claim 6

37. Claim 6 of the '083 patent reads:

The powder according to claim 2, wherein the suspension has less than about 1% of an impurity which is threo-α-phenyl-2-piperidineacetic acid hydrochloride after a period of about 4 months of storage at room temperature.

xxii. '083 Patent, Claim 7

38. Claim 7 of the '083 patent reads:

The powder according to claim 1, wherein the methylphenidate in the immediate release methylphenidate component of (i) comprises about 20% w/w of the total methylphenidate in said powder.

xxiii. '083 Patent, Claim 8

39. Claim 8 of the '083 patent reads:

The powder according to claim 1, wherein the immediate release methylphenidate component comprises an uncoated methylphenidate-ion exchange resin complex.

xxiv. '083 Patent, Claim 12

40. Claim 12 of the '083 patent reads:

The powder according to claim 1, wherein the barrier coating of the sustained release water-insoluble, water-permeable, pH-independent, barrier coated methylphenidate-ion exchange resin complex comprises ethylcellulose.

xxv. '083 Patent, Claim 15

41. Claim 15 of the '083 patent reads:

The powder according to claim 1, wherein the oral aqueous suspension has a therapeutically effective plasma profile for methylphenidate of about 12 hours following a

single oral administration of the oral aqueous suspension to adult subjects under fasted conditions at a dose equivalent to 60 mg racemic methylphenidate HCl.

xxvi. '083 Patent, Claim 16

42. Claim 16 of the '083 patent reads:

The powder according to claim 1, wherein the oral aqueous suspension provides a therapeutically effective amount of methylphenidate within 45 minutes after a single oral administration of the oral aqueous suspension to adult subjects under fasted conditions at a dose equivalent to 60 mg racemic methylphenidate HCl.

xxvii. '083 Patent, Claim 17

43. Claim 17 of the '083 patent reads:

The powder according to claim 1, wherein the oral aqueous suspension provides a single average plasma concentration peak following a single oral administration of the oral aqueous suspension to adult subjects under fasting conditions at a dose equivalent to 60 mg racemic methylphenidate HCl.

(2) <u>The Accused Product</u>

i. ANDA No. 206049 Submitted by Actavis

44. Actavis submitted Abbreviated New Drug Application ("ANDA") No. 206049 to the FDA, pursuant to 21 U.S.C. § 355(j), seeking approval to manufacture and commercially market Methylphenidate HCl Extended Release Oral Suspension, CII ("Actavis's ANDA Product"). The active ingredient in Actavis's ANDA Product is methylphenidate.

45. Actavis's ANDA Product refers to and relies upon the Quillivant XR® NDA and contains data that, according to Actavis, demonstrates that Actavis's ANDA Product is bioequivalent to Qullivant XR® and is a proposed generic version of Quillivant XR®.

46. By letter dated September 3, 2014, Actavis notified Tris that it had filed ANDA No. 206049 and it intended to commercially manufacture, use or sell its ANDA Product before the expiration of, among others, the '765, '033 and '390 patents.

47. By letter dated March 31, 2015, Actavis notified Tris that it intended to commercially manufacture, use or sell its ANDA Product before the expiration of the '649 patent.

48. By letter dated September 9, 2015, Actavis notified Tris that it intended to commercially manufacture, use or sell its ANDA Product before the expiration of the '083 patent.

(3) Infringement

49. For any Asserted Claim for which Actavis stipulates to infringement, or that the court finds would be infringed by a suspension made from Actavis' ANDA Product or the use of that suspension, Actavis does not contest, and stipulates to, induced and contributory infringement of that claim.

i. The '765 Patent

50. Regarding the limitations of claim 1 of the '765 patent, Actavis contests only whether a suspension made from its ANDA product "provides a single mean average plasma concentration peak for methylphenidate."

51. Claim 6 depends from claim 1 of the '765 patent. In addition to the limitation specified above for claim 1 for which Actavis contests infringement, Actavis contests whether a suspension made from its ANDA product has a pharmacokinetic profile that has a "T_{max} of about 4 hours to about 5.25 hours." For the purposes of this litigation, Actavis stipulates that a suspension made from its ANDA product would meet the remaining limitations of claim 6 of the '765 patent.

52. Claim 13 depends from claim 1 of the '765 patent. Other than the limitation specified above for claim 1 for which Actavis contests infringement, for the purposes of this litigation, Actavis stipulates that a suspension made from its ANDA product would meet the remaining limitations of claim 13 of the '765 patent.

53. Claim 16 depends from claim 1 of the '765 patent. Other than the limitation specified above for claim 1 for which Actavis contests infringement, for the purposes of this litigation, Actavis stipulates that a suspension made from its ANDA product would meet the remaining limitations of claim 16 of the '765 patent.

54. Claim 18 depends from claim 17, which depends from claim 1 of the '765 patent. Other than the limitation specified above for claim 1 for which Actavis contests infringement, for the purposes of this litigation, Actavis stipulates that a suspension made from its ANDA product would meet the remaining limitations of claim 18 of the '765 patent.

55. Regarding the limitations of claim 20 of the '765 patent, Actavis contests only whether a suspension made from its ANDA product provides "a single average plasma concentration peak." For the purposes of this litigation, Actavis stipulates that use of a suspension made from its ANDA product would meet the remaining limitations of claim 20 of the '765 patent.

56. Regarding the limitations of claim 25 of the '765 patent, Actavis contests only whether its ANDA product provides "a single mean plasma concentration peak for methylphenidate." For the purposes of this litigation, Actavis stipulates that its ANDA product would meet the remaining limitations of claim 25 of the '765 patent.

57. Claim 30 depends from claim 29, which depends from claim 28, which depends from claim 1 of the '765 patent. Other than the limitation specified above for claim 1 for which Actavis

contests infringement, for the purposes of this litigation, Actavis stipulates that a suspension made from its ANDA product would meet the remaining limitations of claim 30 of the '765 patent.

ii. The '033 patent

58. Regarding the limitations of claim 1 of the '033 patent, Actavis contests only whether a suspension made from its ANDA product has a pharmacokinetic profile that has a "T_{max} of about 4 hours to about 5.25 hours" and "a single mean average plasma concentration peak."

59. Claim 4 depends from claim 1 of the '033 patent. Other than the limitations specified above for claim 1 for which Actavis contests infringement, for the purposes of this litigation, Actavis stipulates that a suspension made from its ANDA product would meet the remaining limitations of claim 4 of the '033 patent.

60. Claim 9 depends from claim 1 of the '033 patent. In addition to the limitations specified above for claim 1 for which Actavis contests infringement, Actavis contests whether a suspension made from its ANDA product has a pharmacokinetic profile that has "a single average plasma concentration peak."

61. Claim 10 depends from claim 9 of the '033 patent. Other than the limitations specified above for claims 1 and 9 for which Actavis contests infringement, for the purposes of this litigation, Actavis stipulates that use of a suspension made from its ANDA product would meet the remaining limitations of claim 10 of the '033 patent.

iii. The '390 patent

62. Regarding the limitations of claim 3 of the '390 patent, Actavis contests only whether a suspension made from its ANDA product "provides a single mean average plasma concentration peak" and has a pharmacokinetic profile that has a "T_{max} of about 4 hours to about 5.25 hours."

63. Claim 15 depends from claim 14, which depends from claim 3 of the '390 patent. Other than the limitations specified above for claim 3 for which Actavis contests infringement, for purposes of this litigation, Actavis stipulates that a suspension made from its ANDA product would meet the remaining limitations of claim 15 of the '390 patent.

64. Regarding the limitations of claim 16 of the '390 patent, Actavis contests only whether a suspension made from its ANDA product "provides a single mean average plasma concentration peak" and has a pharmacokinetic profile that has a "T_{max} of about 4 hours to about 5.25 hours." For purposes of this litigation, Actavis stipulates that a suspension made from its ANDA product would meet the remaining limitations of claim 16 of the '390 patent.

65. Claim 20 depends from claim 3 of the '390 patent. Other than the limitations specified above for claim 3 for which Actavis contests infringement, for the purposes of this litigation, Actavis stipulates that a suspension made from its ANDA product would meet the remaining limitations of claim 20 of the '390 patent.

iv. The '649 patent

66. Regarding the limitations of claim 12 of the '649 patent, Actavis contests only whether a suspension made from its ANDA product "has a single mean average plasma concentration peak" and has a pharmacokinetic profile that has a "T_{max} of about 4 hours to about 5.25 hours." For purposes of this litigation, Actavis stipulates that a suspension made from its ANDA product would meet the remaining limitations of claim 12 of the '649 patent.

67. For the purposes of this litigation, Actavis stipulates to infringement of claim 22 of the '649 patent.

68. For the purposes of this litigation, Actavis stipulates to infringement of claim 23 of the '649 patent.

69. For the purposes of this litigation, Actavis stipulates to infringement of claim 25 of the '649 patent.

70. Regarding the limitations of claim 26 of the '649 patent, Actavis contests only whether a suspension made from its ANDA product "provides a single mean average plasma concentration peak for methylphenidate." For purposes of this litigation, Actavis stipulates that a suspension made from its ANDA product would meet the remaining limitations of claim 26 of the '649 patent.

71. For the purposes of this litigation, Actavis stipulates to infringement of claim 27 of the '649 patent.

72. For the purposes of this litigation, Actavis stipulates to infringement of claim 33 of the '649 patent.

v. The '083 patent

73. For the purposes of this litigation, Actavis stipulates to infringement of claim 5 of the '083 patent.

74. For the purposes of this litigation, Actavis stipulates to infringement of claim 6 of the '083 patent.

75. For the purposes of this litigation, Actavis stipulates to infringement of claim 7 of the '083 patent.

76. For the purposes of this litigation, Actavis stipulates to infringement of claim 8 of the '083 patent.

77. For the purposes of this litigation, Actavis stipulates to infringement of claim 12 of the '083 patent.

78. For the purposes of this litigation, Actavis stipulates to infringement of claim 15 of the '083 patent.

79. For the purposes of this litigation, Actavis stipulates to infringement of claim 16 of the '083 patent.

80. Regarding the limitations of claim 17 of the '083 patent, Actavis contests only whether its ANDA product "provides a single average plasma concentration peak." For purposes of this litigation, Actavis stipulates that its ANDA product would meet the remaining limitations of claim 17 of the '083 patent.

D. State of the Art

81. As of July 2010, methylphenidate was one of the most widely studied and prescribed psychostimulants used to treat ADHD in children. Medical use of methylphenidate began in 1955 as an immediate release ("IR") or short-acting tablets or capsules (*e.g.*, Ritalin). Immediate release methylphenidate ("MPH") formulations are characterized by rapid absorption, low plasma protein binding, and rapid extracellular metabolism. These pharmacokinetic characteristics meant that IR MPH formulations provided clinical benefits within twenty to sixty minutes after dosing and maintained these benefits for around two to four hours.

82. As of July 2010, it was known that methylphenidate underwent typical ester hydrolysis in aqueous solutions.

83. The primary degradation pathway of methylphenidate, through acid- or base catalyzed ester hydrolysis, results in threo-α-phenyl-2-piperidineacetic acid as the major degradation product.

84. As of July 2010, the USP General Notices and Requirements set for a maximum level of impurity for drug products at 2.0%.

85. As of July 2010, it was known that methylphenidate HCl exhibits disproportional and thus linear pharmacokinetics.

86. As of July 2010, a POSA would have known that the prevalence of ADHD in children is greater than in adults, and that children often struggle with swallowing tablets and capsules.

87. As of July 2010, a POSA would have known that solid dosage forms do not permit flexible dose titration that would be available with a liquid formulation.

88. As of July 2010, a POSA would have been aware of drawbacks of immediate release dosage forms of methylphenidate, including that they had to be administered multiple times throughout the day.

94. As of July 2010, a POSA would have known that studies showed that multiple dosing can cause patient adherence issue and complications related to privacy, stigmatization by classmates, potential abuse, and lack of accountability of the school administration.

95. As of July 2010, a POSA would have known that long acting methylphenidate formulations were developed in efforts to provide the efficacy of immediate release formulations, but to allow greater dosing convenience and compliance, minimize security issues at school, and avoid stigmatizing children who are subject to possible ridicule by peers during the school day when additional dosing is required.

96. As of July 2010, a POSA would have recognized that a liquid, extended-release ("ER") formulation was a way to avoid problems with swallowing tablets or capsules and problems with multiple administrations throughout the day, and would have been motivated to develop such a product for the treatment of ADHD.

97. As of July 2010, a POSA would have been motivated to make a liquid ER methylphenidate formulation that had an early onset of action (e.g., 45 minutes) and efficacy that lasted throughout the day (e.g., 12 hours).

98. As of July 2010, a POSA would have been motivated to develop a liquid ER formulation of methylphenidate that was stable.

99. As of July 2010, a POSA would have known that methylphenidate has a half-life of about 2-3 hours.

100. As of July 2010, the prior art disclosed barrier coatings, including water insoluble, water-permeable, and pH-independent barrier coatings for the preparation of extended release products, including ethylcellulose, methacrylic acid, methyl methacrylate, and a polyvinylacetate polymer in combination with a plasticizer.

101. As of July 2010, the prior art disclosed that ion-exchange resin-complex technology can be used to make extended-release products, including liquid formulations.

102. As of July 2010, the prior art taught that ion-exchange resin-complexes can be prepared as a matrix using a hydrophilic polymer agent, including polyvinylpyrrolidone.

103. As of July 2010, commercially available controlled-release methylphenidate products included CONCERTA, DAYTRANA, FOCALIN, METADATE CD, METHYLIN ER, RITALIN LA, and RITALIN-SR.

104. RITALIN SR was approved by the FDA in 1982.

105. The 2007 revision of the RITALIN SR prescribing information was publicly available in 2007.

106. The "Product Literature, Ritalin® hydrochloride methylphenidate hydrochloride tablets USP and Ritalin-SR® methylphenidate hydrochloride USP sustained-release tablets, revised Dec. 2010" is cited in the specification of the patents-in-suit.

107. RITALIN-SR is a sustained-released tablet.

108. According to Patrick et al., "New Methylphenidate Formulations for the Treatment of Attention-Deficit/Hyperactivity Disorder," Expert Opin. Drug Deliv., 2(1):121-143 (2005) ("Patrick 2005"), RITALIN-SR and a generic sustained-release product can have the following mean concentration-time profile at a dose of 20 mg (RITALIN SR in closed squares and generic sustained-release product in open circles):

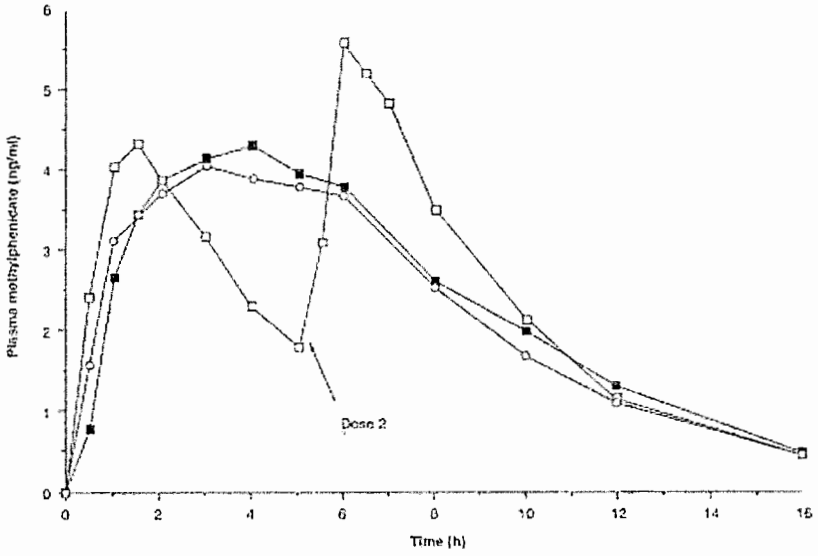


Figure 5. Pharmacokinetic profile of immediate-release methylphenidate (10 mg b.i.d.) compared with that of the Ritalin-SR® (20 mg) and the generic sustained-release product (20 mg). Mean concentration-time profiles (n = 18) comparing two 20 mg SR-MPH (closed squares, circles) formulations versus IR-MPH (open squares) dosed twice daily. From PATRICK KS, STRAUGHN AB, WARM EJ, BREESE GR, MEYER MC: The absorption of sustained-release methylphenidate formulations compared to an immediate-release formulation. *Biopharm. Drug Dispos.* **10**:165–171, copyright (1989). Copyright John Wiley & Sons Ltd. Reproduced with permission.

109. This figure is also provided in Markowitz, J. et al., "Advances in the Pharmacotherapy of Attention-Deficit–Hyperactivity Disorder: Focus on Methylphenidate Formulations," Pharmacotherapy, 23(10) at 1281-1299 (2003) published in 2003 ("Markowitz"), which is cited on the face of each of the patents-in-suit.

110. Biederman, J. "New Generation Long-Acting Stimulants for the Treatment of Attention-Deficit/Hyperactivity Disorder," Medscape Psychiatry, 8(2) (Nov. 2003) published in 2003 ("Biederman").

111. Swanson, J., et al., Development of a New Once-a-Day Formulation of Methylphenidate for the Treatment of Attention-deficit/Hyperactivity Disorder, Arch GenPsychiatry 60:204-211 (2003) ("Swanson 2003") states the following with respect to Ritalin-SR: "This SR methylphenidate formulation was approved for the treatment of ADHD over a decade ago, but it had delayed onset of action and reduced efficacy compared with the IR methylphenidate formulation and was not well accepted in clinical practice."

112. U.S. Patent Application Publication No. 2010/0260844 ("Scicinski") published on October 14, 2010. Scicinski is cited on the face of each of the patents-in-suit. According to Scicinski, "based on PK parameters, the Ritalin SR product has a slower onset and shorter duration than two IR methylphenidate doses."

113. CONCERTA was approved by the FDA in 2000.

114. METADATE CD was approved by the FDA in 2001.

115. FOCALIN XR was approved by the FDA in 2005.

116. DAYTRANA was approved by the FDA in 2006.

117. The prescribing information for CONCERTA, METADATE CD, FOCALIN XR, and DAYTRANA from the 64th Ed. PDR published in 2009, more than one year before the filing date of the asserted patents.

118. The "Product Literature, Concerta®, (methylphenidate HCl) Extended-release Tablets, rev Nov. 2010" is cited in the specification of the patents-in-suit.

119. The "Product Literature, Once Daily Metadate CD™ (methylphenidate HCl, USP) Extended-Release Capsules, Feb. 2007" is cited in the specification of the patents-in-suit.

120. The "Ritalin-LA®, Product Label, Dec. 13, 2013" is cited in the specification of the patents-in-suit.

121. The "Product Literature, Focalin™ XR (dexmethylphenidate hydrochloride) extended-release capsules, 2004" is cited in the specification of the patents-in-suit.

122. The "Product Literature, Daytrana™ (methylphenidate transdermal system), revised Dec. 2009" is cited in the specification of the patents-in-suit.

123. CONCERTA is an extended release tablet.

124. According to the CONCERTA prescribing information, CONCERTA has the following plasma concentration profile at a dose of 18 mg:

FIGURE 1

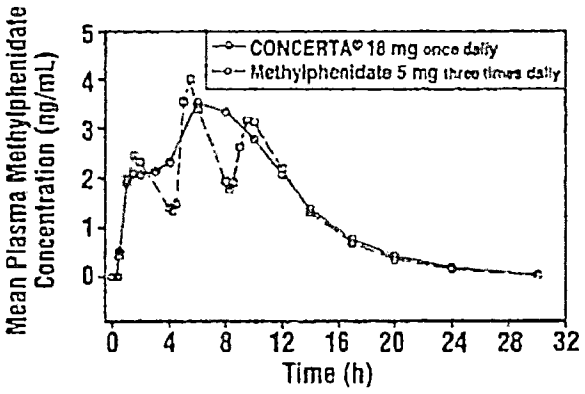


Figure 1. Mean methylphenidate plasma concentrations in 36 adults, following a single dose of CONCERTA® 18 mg once daily and immediate-release methylphenidate 5 mg three times daily administered every 4 hours.

TABLE 6. Pharmacokinetic Parameters (Mean ± SD) After Single Dose in Healthy Adults

Parameters	CONCERTA® (18 mg once daily) (n=36)	Methylphenidate (5 mg three times daily) (n=35)
C_{max} (ng/mL)	3.7 ± 1.0	4.2 ± 1.0
T_{max} (h)	6.8 ± 1.8	6.5 ± 1.8
AUC_{inf} (ng•h/mL)	41.8 ± 13.9	38.0 ± 11.0
$t_{1/2}$ (h)	3.5 ± 0.4	3.0 ± 0.5

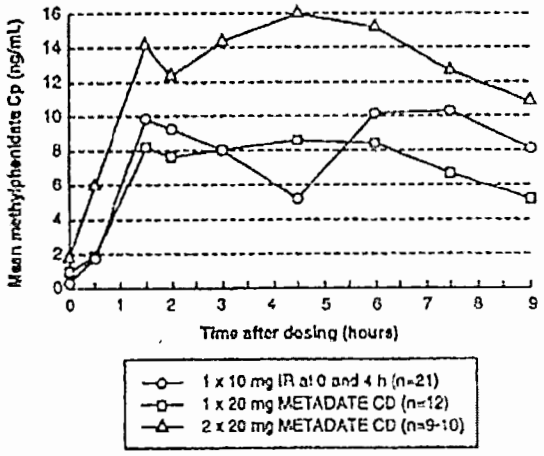
125. The prescribing information for CONCERTA does not state that CONCERTA can be subdivided or sprinkled onto applesauce. The ratio of immediate release methylphenidate to sustained-release methylphenidate in CONCERTA is 22:78. This information is provided in Markowitz, which is referenced above.

126. METADATE CD is a capsule.

127. According to the METADATE CD prescribing information, METADATE CD has the following plasma concentration profile:

FIGURE 1

Comparison of Immediate Release (IR) and METADATE CD Formulations After Repeated Doses of Methylphenidate HCl in Children with ADHD



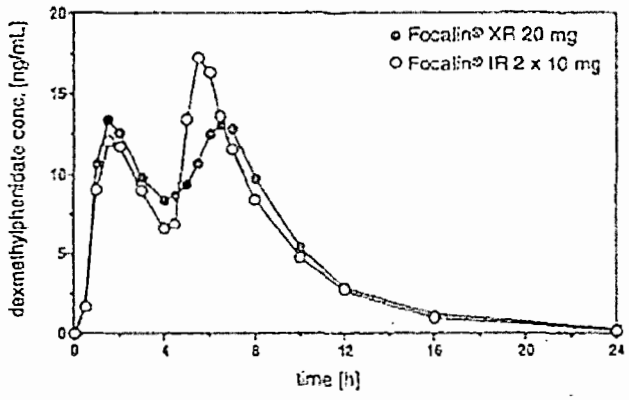
128. The prescribing information for METADATE CD says that the METADATE CD capsule may be opened and the contents sprinkled on applesauce, and that the mixture should be given immediately and not stored for future use.

129. The ratio of immediate release methylphenidate to sustained-release methylphenidate in METADATE CD is 30:70.

130. FOCALIN XR is an extended release capsule.

131. The ratio of immediate release d-methylphenidate to delayed-release d-methylphenidate in FOCALIN XR is 50:50. According to the FOCALIN XR prescribing information, FOCALIN XR has the following plasma concentration profile:

Figure 1. Mean Dexmethylphenidate Plasma Concentration-Time Profiles After Administration of 1 x 20 mg Focalin XR (n=24) Capsules and 2 x 10 mg Focalin Immediate-Release Tablets (n=25)



132. According to the prescribing information for FOCALIN XR, FOCALIN XR capsules be may opened and its contents sprinkled on applesauce, and that the mixture of drug and applesauce should be consumed immediately in its entirety and not stored for future use.

133. The RITALIN LA prescribing information from the 60th Ed. PDR published in 2005.

134. RITALIN LA is a capsule.

135. The ratio of immediate release methylphenidate to delayed-release methylphenidate in RITALIN LA is 50:50.

136. According to the RITALIN LA prescribing information, RITALIN LA has the following plasma concentration profile:

Figure 1. Mean plasma concentration time-profile of methylphenidate after a single dose of Ritalin® LA 40 mg q.d. and Ritalin® 20 mg given in two doses four hours apart

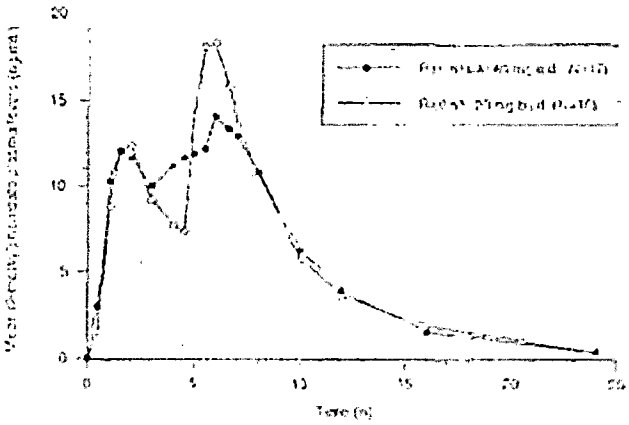


Table 1
Mean ± SD and range of pharmacokinetic parameters of methylphenidate after a single dose of Ritalin LA® and Ritalin® given in two doses 4 hours apart

Population	Children		Adult Males	
Formulation Dose N	Ritalin® 10 mg & 10 mg 21	Ritalin LA® 20 mg 10	Ritalin® 10 mg & 10 mg 9	Ritalin LA® 20 mg 8
T_{lag} (h)	0.24 ± 0.44 0-1	0.50 ± 0.40 0-1	1.0 ± 0.5 0.5-1.5	0.7 ± 0.2 0.5-1.0
T_{max1} (h)	1.6 ± 0.6 1-3	2.0 ± 0.8 1-3	1.9 ± 0.4 1.5-2.7	2.0 ± 0.9 1.0-4.0
C_{max1} (ng/mL)	10.3 ± 4.2 4.3-20.2	10.3 ± 5.1 5.4-25.6	4.0 ± 2.3 1.8-7.5	5.3 ± 0.9 3.8-6.9
T_{min2} (h)	4.0 ± 0.2 4-5	4.5 ± 1.2 3-6	3.8 ± 0.4 3.5-4.3	3.6 ± 0.6 2.7-4.3
C_{min2} (ng/mL)	5.6 ± 2.7 3.1-14.1	8.1 ± 4.1 2.4-21.0	1.9 ± 1.4 0.6-3.7	3.0 ± 0.8 1.7-4.0
T_{max2} (h)	5.6 ± 0.7 5-8	6.6 ± 1.5 5-11	5.9 ± 0.5 5.0-6.5	5.5 ± 0.8 4.5-6.5
C_{max2} (ng/mL)	15.3 ± 7.0 6.9-32.8	16.2 ± 5.9 4.3-31.1	6.9 ± 1.4 3.6-7.9	6.2 ± 1.4 3.9-8.3
$AUC_{0-\infty}$ (ng/mL × h) $t_{1/2}$ (h)	102 ± 54.5 40.6-251.6 3.5 ± 0.6 1.9-5.0	86.5 ± 64.0* 43.9-364.44 2.4 ± 0.7* 1.5-4.0	37.9 ± 21.0 14.2-85.0 0.5 ± 1.9 1.0-7.7	45.5 ± 10.0 34.6-61.0 3.3 ± 0.4 3.0-4.2

* N = 15

137. The prescribing information for RITALIN LA states that RITALIN LA capsules may be carefully opened and the beads sprinkled over a spoonful of applesauce, and that the mixture of drug and applesauce should be consumed immediately in its entirety and not stored for future use.

138. METHYLIN Oral Solution was approved by the FDA in 2002.

139. The 2006 revision of the METHYLIN Oral Solution label was publicly available in 2006. Methylin® Oral Solution is discussed in the specification of the patents-in-suit.

140. METHYLIN Oral Solution has the following plasma concentration profile:

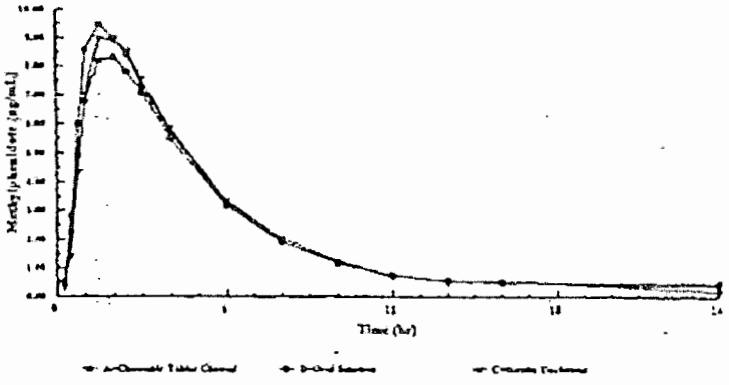


Figure 11.5-1: Mean Plasma Concentration Profile of Methylphenidate Formulations (20 mg)

Table 3.1.2
Summary of Untransformed Pharmacokinetic Data
[Mean (SD)]

Parameter	Treatment Groups		
	MPH HCl Chewable Tablet (A)	MPH HCl Oral Solution (B)	Ritalin® Tablet Unchewed (C)
N	32	33	34
AUCinf (ng·hr/mL)	48.97 (16.23)	46.70 (15.58)	47.65 (14.20)
AUCt (ng·hr/mL)	46.32 (15.95)	45.10 (15.37)	46.01 (14.35)
Cmax (ng/mL)	9.982 (2.677)	9.675 (2.610)	9.834 (2.723)
Kel (1/hr)	0.2515 (0.0363)	0.2604 (0.0385)	0.2579 (0.0374)
T1/2 (hr)	2.826 (0.516)	2.725 (0.449)	2.755 (0.506)
Tmax (hr)	1.530 (0.413)	1.712 (0.577)	1.863 (0.432)

Reference: Tables 14.2.1-4 through 14.2.1-10 of Methylphenidate Study 010

141. Swanson, J.M., et al., "A Comparison of Once-Daily Extended-Release Methylphenidate Formulations in Children With Attention- Deficit/Hyperactivity Disorder in the Laboratory School (The Comacs Study)," Pediatrics, 113(3): 206-16 (2004) ("Swanson 2004") published in 2004.

142. Swanson reported a study comparing CONCERTA and METADATE CD and showed that METADATE CD (with more immediate release component) provided better therapeutic results soon after dosing, while CONCERTA (with more controlled release component) provided better therapeutic results later in the day (up to 12 hours).

143. Chavez, B. et al., "An Update on Central Nervous System Stimulant Formulations in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder," The Annals of Pharmacotherapy; 43:1084-1095 (June 2009) ("Chavez") published in 2009.

144. Allen, L. et al., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems (Lippincott Williams & Wilkins, 8th ed. 2005) ("Ansel's") published in 2005.

145. U.S. Patent Application Publication No. 2007/0215511 ("Mehta") published on September 20, 2007. Mehta is cited on the face of each of the patents-in-suit.

146. International Application Publication No. WO 2008/064163 ("Chen") published on May 29, 2008. Chen is cited on the face of each of the patents-in-suit.

147. U.S. Patent Application No. 2003/0099711 ("Meadows") published on May 29, 2003. Meadows is cited on the face of each of the patents-in-suit.

148. U.S. Patent No. 7,691,880 ("Herman") was filed October 7, 2004 and issued on April 6, 2010. Herman is cited on the face of each of the patents-in-suit.

149. Connors et al., Chemical Stability of Pharmaceuticals: A Handbook for Pharmacists (John Wiley & Sons 2nd ed. 1986) published in 1986 ("Connors"). Connors is cited on the face of the '649 and '083 patents.

150. González et al., "Methylphenidate Bioavailability from Two Extended-Release Formulations," Int'l J. Clin. Pharmacology & Therapeutics, 40(4):175-184 (2002) ("Gonzalez") published in 2002.

151.

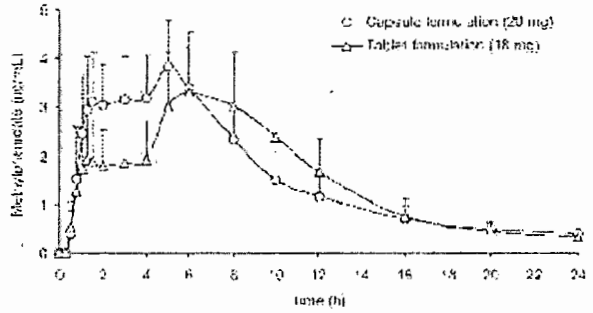


Figure 1 Methylphenidate plasma concentration-time profiles following the administration of one 20 mg capsule and one 18 mg tablet. Data represent the mean ± SD, n = 35.

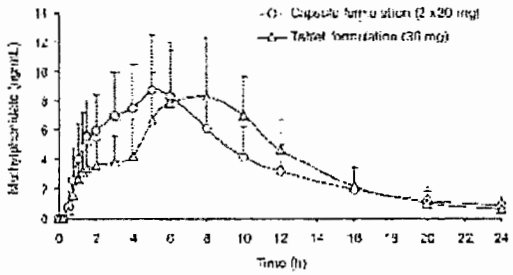


Figure 2a.

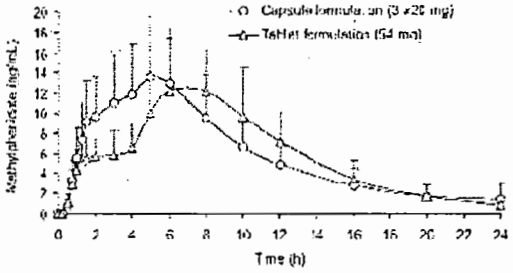


Figure 2b.

Figure 2a, b. Methylphenidate plasma concentration-time profiles following the administration of (2a) 2 × 20 mg capsules and one 36 mg tablet and (2b) 3 × 20 mg capsules and one 54 mg tablet. Data represent the mean ± SD, n = 21.

Table 2. Methylphenidate pharmacokinetic parameters and plasma concentrations following the administration of one 20 mg capsule or one 18 mg tablet (n = 35).

			Unadjusted			Dose-normalized[a]		
	Capsule (mean ± SD)	Tablet (mean ± SD)	Mean Ratio[b]	90% CI[c]	Tablet (mean ± SD)	Mean Ratio[b]	90% CI[c]
PK parameter:							
AUC_{0-last} (ng × h/ml)	36.31 (10.92)	34.63 (13.15)	97.00	93.37, 100.78	38.47 (14.61)	107.78	103.74, 111.97
$AUC_{0-\infty}$ (ng × h/ml)	39.74 (11.75)	36.43 (13.50)	93.41	90.12, 96.81	40.48 (15.01)	103.78	100.13, 107.57
C_{max-1} (ng/ml)	3.33 (0.94)	2.08 (0.99)	61.84	58.00, 65.94	2.32 (1.10)	68.71	64.44, 73.26
C_{max-2} (ng/ml)	3.89 (0.99)	3.43 (1.19)	89.45	84.44, 94.76	3.81 (1.32)	99.39	93.82, 105.29
AUC_{0-t} (ng × h/ml)	10.01 (3.06)	6.28 (2.65)	62.92	59.60, 66.43	6.98 (2.95)	69.92	66.24, 73.82
AUC_{0-6} (ng × h/ml)	17.11 (4.65)	11.90 (4.50)	70.14	66.78, 73.66	13.23 (5.00)	77.94	74.21, 81.85
AUC_{0-8} (ng × h/ml)	22.78 (6.01)	18.21 (6.55)	80.86	77.28, 84.60	20.23 (7.28)	89.85	85.89, 94.00
$t_{1/2}$ (h)	6.24 (1.32)	3.58 (0.68)	NA[d]	NA	NA	NA	NA
Plasma methylphenidate concentration (ng/ml):							
1 h	2.48 (1.19)	1.75 (0.88)	72.52	62.28, 84.43	1.95 (0.98)	80.49	69.14, 93.72
1.5 h	3.11 (1.02)	1.90 (0.83)	61.64	57.57, 66.00	2.11 (0.92)	68.42	63.90, 73.26
3 h	3.14 (0.89)	1.86 (0.79)	59.04	55.25, 63.08	2.06 (0.88)	65.53	61.33, 70.02
4 h	3.17 (0.90)	1.94 (0.79)	61.69	57.47, 66.22	2.15 (0.87)	68.47	63.79, 73.50
6 h	3.40 (0.84)	3.30 (1.24)	97.70	91.70, 104.11	3.68 (1.38)	108.45	101.78, 115.56
8 h	2.35 (0.77)	3.02 (1.11)	132.72	125.67, 140.16	3.35 (1.23)	147.31	139.49, 155.58
10 h	1.53 (0.58)	2.40 (0.89)	165.07	156.21, 174.43	2.66 (0.99)	183.23	173.39, 193.62
12 h	1.17 (0.46)	1.68 (0.71)	148.90	140.97, 157.27	1.86 (0.79)	165.28	156.47, 174.57

[a]Pharmacokinetic parameters were dose-normalized to the capsule formulation by a factor of 1.11.
[b]Mean ratios were calculated based on least-squares means with the capsule formulation as the reference.
[c]CI based on log-transformed data converted to original scale and expressed as a percentage.
[d]Not applicable.

Table 3. Methylphenidate pharmacokinetic parameters and plasma concentrations following the administration of two 20 mg capsules or one 36 mg tablet (n = 21).

	Unadjusted				Dose-normalized[a]			
	Capsule (mean ± SD)	Tablet (mean ± SD)	Mean Ratio[b]	90% CI[c]	Tablet (mean ± SD)	Mean Ratio[b]	90% CI[c]
PK parameter:							
AUC_{0-last} (ng × h/ml)	89.19 (44.21)	90.58 (42.04)	102.20	98.14, 106.43	100.54 (46.66)	113.44	108.93, 118.14
$AUC_{0-\infty}$ (ng × h/ml)	98.49 (52.05)	94.05 (44.51)	97.20	93.33, 101.22	104.40 (49.41)	107.89	103.59, 112.36
C_{max-1} (ng/ml)	6.04 (1.92)	4.06 (1.73)	60.23	54.67, 66.36	4.51 (1.92)	66.85	60.68, 73.68
C_{max-2} (ng/ml)	7.42 (1.68)	8.63 (3.76)	100.25	93.12, 107.93	9.58 (4.20)	111.28	103.36, 119.80
AUC_{0-t} (ng × h/ml)	20.36 (8.74)	11.68 (5.68)	57.48	54.19, 60.98	13.19 (6.51)	63.80	60.15, 67.68
AUC_{0-6} (ng × h/ml)	37.03 (15.27)	24.59 (11.84)	65.00	61.27, 68.96	27.30 (13.15)	72.15	68.01, 76.54
AUC_{0-8} (ng × h/ml)	51.44 (21.70)	40.97 (19.06)	78.48	73.84, 83.41	45.47 (21.15)	87.11	81.96, 92.59
$t_{1/2}$ (h)	6.82 (2.23)	3.84 (0.72)	NA[d]	NA	NA	NA	NA
Plasma methylphenidate concentration (ng/ml):							
1 h	4.03 (2.43)	2.63 (1.64)	65.23	57.02, 74.62	2.91 (1.81)	72.41	63.29, 82.83
1.5 h	5.58 (2.48)	3.41 (1.60)	60.64	55.36, 66.43	3.78 (1.78)	67.31	61.44, 73.74
3 h	6.97 (2.97)	3.80 (1.81)	53.75	49.71, 58.11	4.22 (2.01)	59.66	55.18, 64.50
4 h	7.45 (3.04)	4.23 (2.55)	53.56	50.26, 57.07	4.69 (2.83)	59.45	55.79, 63.35
6 h	8.33 (3.59)	7.84 (3.56)	93.18	85.21, 101.89	8.71 (3.94)	103.43	94.58, 113.10
8 h	6.11 (2.95)	8.32 (4.06)	135.37	124.50, 147.18	9.23 (4.51)	150.26	138.20, 163.37
10 h	4.14 (2.10)	6.96 (2.67)	173.10	163.25, 183.54	7.73 (2.97)	192.14	181.21, 203.73
12 h	3.14 (1.92)	4.68 (2.03)	155.29	144.23, 167.21	5.20 (2.25)	172.37	160.09, 185.60

[a]Pharmacokinetic parameters were dose-normalized to the capsule formulation by a factor of 1.11.
[b]Mean ratios were calculated based on least-squares means with the capsule formulation as the reference.
[c]CI based on log-transformed data converted to original scale and expressed as a percentage.
[d]Not applicable.

Table 4. Methylphenidate pharmacokinetic parameters and plasma concentrations following the administration of three 20 mg capsules or one 54 mg tablet (n = 21).

	Unadjusted				Dose-normalized[a]			
	Capsule (mean ± SD)	Tablet (mean ± SD)	Mean Ratio[b]	90% CI[c]	Tablet (mean ± SD)	Mean Ratio[b]	90% CI[c]
PK parameter:							
AUC_{0-last} (ng × h/ml)	138.74 (60.51)	137.61 (60.47)	99.17	95.22, 103.27	152.75 (67.13)	110.08	105.70, 114.63
$AUC_{0-\infty}$ (ng × h/ml)	145.34 (65.21)	143.38 (64.83)	94.88	91.03, 98.90	159.15 (71.96)	105.32	101.05, 109.77
C_{max-1} (ng/ml)	10.38 (3.32)	8.00 (2.19)	56.25	50.90, 62.16	8.88 (2.43)	62.44	56.50, 69.00
C_{max-2} (ng/ml)	12.41 (3.17)	12.60 (5.51)	91.03	84.36, 98.23	13.99 (6.12)	101.05	93.64, 109.04
AUC_{0-t} (ng × h/ml)	32.01 (13.09)	18.81 (7.18)	59.01	55.63, 62.60	20.88 (7.97)	65.50	61.75, 69.48
AUC_{0-6} (ng × h/ml)	58.12 (24.12)	38.24 (15.30)	65.98	62.19, 70.00	42.44 (16.98)	73.24	69.03, 77.69
AUC_{0-8} (ng × h/ml)	80.73 (33.15)	62.70 (25.73)	77.56	72.97, 82.43	69.59 (28.56)	86.09	81.00, 91.50
$t_{1/2}$ (h)	6.37 (1.22)	4.07 (0.76)	NA[d]	NA	NA	NA	NA
Plasma methylphenidate concentration (ng/ml):							
1 h	5.53 (3.03)	4.35 (2.06)	83.01	73.35, 96.00	4.83 (2.29)	93.14	81.42, 106.56
1.5 h	9.19 (4.06)	5.48 (2.15)	60.89	55.58, 66.70	6.08 (2.39)	67.58	61.69, 74.04
3 h	11.11 (4.96)	5.87 (2.38)	53.56	49.54, 57.91	6.52 (2.65)	59.45	54.99, 64.28
4 h	11.92 (5.03)	6.50 (2.69)	54.27	50.93, 57.83	7.21 (2.98)	60.24	56.53, 64.19
6 h	13.01 (5.60)	12.28 (5.18)	94.73	86.63, 103.59	13.64 (5.75)	105.15	96.15, 114.98
8 h	9.61 (4.21)	12.18 (5.71)	125.61	115.71, 136.78	13.52 (6.34)	139.65	128.44, 151.83
10 h	6.57 (2.94)	9.71 (4.71)	146.70	138.36, 155.55	10.77 (5.23)	162.84	153.58, 172.66
12 h	4.90 (2.35)	7.13 (3.04)	148.01	137.47, 159.37	7.92 (3.38)	164.29	152.59, 176.90

[a]Pharmacokinetic parameters were dose-normalized to the capsule formulation by a factor of 1.11.
[b]Mean ratios were calculated based on least-squares means with the capsule formulation as the reference.
[c]CI based on log-transformed data converted to original scale and expressed as a percentage.
[d]Not applicable.

152. Gonzalez states in part: "The plasma concentration-time profiles for the capsule [METADATE CD] and tablet [CONCERTA] formulations exhibited biphasic characteristics, regardless of dosage, consisting of a sharp initial increase followed by a second increase in MPH plasma levels – resulting in two peak plasma concentrations (C_{max-1} and C_{max-2})."

153. U.S. Patent No. 6,419,960 ("Krishnamurthy") issued on July 16, 2002.

154. Cascade, E. et al., "Short-acting versus Long-acting Medications for the Treatment of ADHD," Psychiatry (Edgemont) 2008; 5(8):24-27 ("Cascade") published in 2008.

155. Patrick 2005 published in 2005.

156. Patrick et al., "Evolution of Stimulants to Treat ADHD: Transdermal Methylphenidate," Hum. Psychopharmacology, 24(1):1-17 (Jan. 2009) ("Patrick 2009") published in 2009.

157. U.S. Patent No. 8,062,667 ("the '667 patent"), entitled "Modified Release Formulations Containing Drug-Ion Exchange Resin Complexes," issued on November 22, 2011.

158. The '667 patent is cited on the face of each of the patents-in-suit. The '667 patent expires on March 29, 2029.

159. The named inventors on the '667 patent are Ketan Mehta and Yu-Hsing Tu, both of whom are among the named inventors of the patents-in-suit. The '667 patent identifies Tris as the assignee of the '667 patent, who is also identified as the assignee of the patents-in-suit.

160. Claim 1 of the '667 patent states:

> An aqueous pharmaceutical suspension composition suitable for oral ingestion comprising:
> (i) a particulate matrix comprising a particulate drug-ion exchange resin complex and a water insoluble polymer or copolymer, or hydrophilic polymer, said particulate matrix capable of passing through a number 40 mesh screen,
> said drug-ion exchange resin complex comprising a pharmaceutically acceptable drug bound to a pharmaceutically acceptable water insoluble ion exchange resin to form said drugion exchange resin complex, said ion exchange resin being selected from
> (A) a sulfonated copolymer comprising styrene and divinylbenzene, and
> (B) a copolymer comprising styrene and divinylbenzene having quaternary ammonium functional groups,
> wherein said water insoluble polymer or copolymer, or hydrophilic polymer is present in an amount of about 3% to about 30% by weight, based on the weight of said drug-ion exchange resin complex
> (ii) a cured, high tensile strength, water permeable, water insoluble, non-ionic polymeric diffusion barrier coating over said particulate drug-ion exchange resin complex—water insoluble polymer or copolymer, or hydrophilic polymer matrix defined in (i), said cured barrier coating applied as an aqueous dispersion and Comprising
> (a) a polyvinylacetate polymer
> (b) a stabilizer, and
> (c) at least an amount of plasticizer effective to enhance the tensile strength of said cured barrier coating, whereby said barrier coating provides a modified release profile to said pharmaceutically acceptable drug in said drug-ion exchange resin complex in said

matrix and
(iii) a pharmaceutically acceptable aqueous suspension base wherein said particulate drug-ion exchange resin complex and said water insoluble polymer or copolymer, or hydrophilic polymer covered with said cured barrier coating as defined in (ii) is suspended in said aqueous suspension base.

161. Claim 6 of the '667 patent states:

The aqueous suspension composition according to claim 1, further comprising an orally ingestible drug bound to a pharmaceutically acceptable, water insoluble ion exchange resin to form an uncoated particulate drug-ion exchange resin complex, said ion exchange resin in the uncoated complex being a sulfonated copolymer comprising styrene and divinylbenzene, and wherein said drug in said uncoated complex is either the same as or different from the pharmaceutically acceptable drug in (i) and said uncoated complex being of a size capable of passing through a number 40 mesh screen.

162. Claim 8 of the '667 patent states:

The aqueous suspension composition according to claim 6, wherein said drug in said uncoated drug-ion exchange resin complex is the same as the pharmaceutically acceptable drug in (i).

163. Claim 9 of the '667 patent states:

The aqueous suspension composition according to claim 8, wherein said drug in said uncoated drug-ion exchange resin complex is a methylphenidate.

a. Procedural History

164. On October 15, 2014, Tris sued Actavis for infringement of the '765, '033 and '390 patents (Civ. Action No. 14-1309).

165. On May 15, 2015, Tris sued Actavis for infringement of the '649 patent (Civ. Action No. 15-0393). The case was consolidated with Civil Action No. 14-1309.

166. On October 23, 2015 Tris sued Actavis for infringement of the '083 patent (Civ. Action No. 15-0969). The case was consolidated with Civil Action No. 14-1309.

167. On January 8, 2016, the court issued an order construing the terms of the patents-in-suit. (D.I. 95.) The court construed the term "single mean average plasma concentration peak" in accordance with its plain and ordinary meaning.

168. The court held a bench trial on February 6 through February 10, 2017. Actavis argued that Tris failed to meet its burden of proving infringement of the Single Peak claims. Actavis also argued that all asserted claims are invalid as obvious under 35 U.S.C. § 103.

169. At the close of Tris's prima facie case of infringement of the asserted patents, Actavis moved pursuant to Federal Rule of Civil Procedure 52(c) for judgment of noninfringement on the Single Peak claim limitations. At the close of Actavis's case on defense on infringement, Tris moved pursuant to Federal Rule of Civil Procedure 52(c) for judgment of infringement. The court reserved judgment on both motions.

III. DISCUSSION AND CONCLUSIONS OF LAW

The court has subject matter jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331 and 1338(a), 2201, and 2202. Venue is proper in this court under 28 U.S.C. §§ 1391(b) and (c), and 1400(b). After having considered the entire record in this case, the substantial evidence in the record, the parties' post-trial submissions, and the applicable law, the court concludes that all asserted claims of the patents-in-suit are invalid. The court's reasoning follows.

A. Obviousness[2]

Actavis challenges the validity of the asserted claims of the '765, '033, '390, '649, and '083 patents, arguing that a POSA would have found it obvious in light of the prior art to synthesize Qullivant XR® as an improved ADHD treatment.

At the outset, the parties agree that at the time of the invention, a POSA would have been motivated to make an extended release liquid methylphenidate product with an early onset of action and extended duration of effect. (D.I. 141 ¶ 137.) Actavis therefore contends that a POSA would have had both a motivation and more than a reasonable expectation of success in achieving that goal. The court finds, for the reasons that follow, that Actavis has established by clear and convincing evidence that the patents-in-suit are obvious.

[2] The court acknowledges that Actavis asserted the affirmative defenses of non-infringement and obviousness-type double patenting. Because the court has found all asserted claims of the patents-in-suit invalid as obvious, it declines to address Actavis's other affirmative defenses.

(1) The Legal Standard

35 U.S.C. § 103(a) provides that a patent may not be obtained "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious to a person having ordinary skill in the art." Obviousness is a question of law that is predicated on several factual inquires. *See Richardson-Vicks v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed. Cir. 1997). The trier of fact is directed to assess four considerations: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) secondary considerations of nonobviousness, such as commercial success, long-felt but unsolved need, failure of others, acquiescence of others in the industry that the patent is valid, and unexpected results. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

"A patent shall be presumed valid." 35 U.S.C. § 282. A party seeking to challenge the validity of a patent based on obviousness must demonstrate by clear and convincing evidence[3] that the invention described in the patent would have been obvious to a person of ordinary skill in the art at the time the invention was made. Importantly, in determining what would have been obvious to one of ordinary skill in the art, the use of hindsight is not permitted. *See KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007) (cautioning the trier of fact against "the distortion caused by hindsight bias" and "arguments reliant upon ex post reasoning" in determining obviousness). In *KSR*, the Supreme Court rejected the rigid application of the principle that there should be an explicit teaching, suggestion, or motivation in the prior art, the "TSM test," in order to find obviousness. *See id.* at 415. The *KSR* Court acknowledged, however, the importance of

[3] "Clear and convincing evidence is evidence that places in the fact finder an abiding conviction that the truth of [the] factual contentions are highly probable." *Alza Corp v. Andrx Pharms., LLC,* 607 F. Supp. 2d 614, 631 (D. Del. 2009) (internal quotations omitted) (quoting *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984)).

identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *Id.* at 418.

"Obviousness does not require absolute predictability of success," but rather, requires "a reasonable expectation of success." *See Medichem, S.A. v. Rolado, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (quoting *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988)). To this end, obviousness "cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Moreover, while the Federal Circuit has noted that pharmaceuticals can be an "unpredictable art" to the extent that results may be unexpected, it also recognizes that, per *KSR*, evidence of a "finite number of identified, predictable solutions" or alternatives "might support an inference of obviousness." *See Eisai Co. Ltd. v. Dr. Reddy's Labs. Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008).

(2) The Level of Ordinary Skill in the Art

A person of ordinary skill in the art ("POSA") with respect to the patents-in-suit would have an advanced degree in pharmaceutical, chemical, or medical sciences (or the equivalent) and 3 to 5 years working in the field(s) of pharmaceutical formulation and/or treatment of conditions susceptible to treatment with methylphenidate. A POSA would also rely as needed on pharmacokineticists and clinicians who have at least 3 to 5 years' experience with ADHD and would have the ability to understand work presented and published by pharmacokineticists and clinicians regarding ADHD.[4]

[4] The court's definition is drawn from the testimony of Dr. James John McGough. (Tr. 663:4-22.) While Actavis proposed a slightly different definition than that of Dr. McGough, all doctors testified that their opinions on obviousness would not change, regardless of whose definition of a POSA applied. (Tr. 361:3-14 (Straughn); Tr. 449:3-12 (Moreton); Tr. 663:23-664:1 (McGough); Tr. 835:13-18 (Jacobs).)

(3) The Scope and Content of the Prior Art and Differences Between the Claimed Subject Matter and the Prior Art

a. Aqueous MPH Formulation

Initially, the court analyzes whether the claimed Aqueous MPH formulation would have been obvious. Actavis argues that the prior art taught how to make stable liquid methylphenidate formulations having the pharmacokinetic characteristics and formulation details of the asserted claims. Specifically, Actavis relies on the combination of the Mehta (JTX-40), Ansel's (JTX-17), and Connors (JTX-24) references. The Mehta reference discloses the use of ion exchange resin technology to make extended release formulations, including aqueous suspensions. (JTX-40 ¶¶ 2, 26.) Mehta specifically identifies methylphenidate as an active ingredient that can be used with the disclosed ion exchange resin technology. (D.I. 152 at 12.)

Actavis also contends that Mehta discloses the following formulation details in the asserted claims: (1) formulation of ion exchange resin complexes in the form of a powder for reconstitution; (2) immediate release and barrier-coated sustained release ion exchange resin complexes; (3) specific barrier coatings including polyvinyl acetate with plasticizer; (4) the hydrophilic polymer polyvinylpyrrolidone as a matrix forming polymer in an amount of 5% to 20% by weight; (5) buffering agents; (6) poloxamer surfactants; (7) sweeteners; and (8) preservatives. (D.I. 152 at 12.) According to Actavis, Mehta also teaches that the disclosed ion exchange resin technology can be tailored to provide "a pre-determined release profile of a drug from the drug-ion exchange resin complex for up to about 24 hours." (JTX-40 ¶¶ 2, 26.) Based upon the teachings of Mehta, Actavis argues a POSA would have understood that the technology could be used to make formulations having early onset of action and prolonged effect. (D.I. 152 at 13.)

Furthermore, Actavis's expert, Dr. Moreton, explained that Ansel's would have taught a POSA exactly how to avoid hydrolysis and formulate a stable extended release liquid

methylphenidate product. (JTX-17 at 25, 69-70; Tr. 454:6-11, 462:12-463:3, 472:6-13 (Moreton).) Dr. Moreton highlighted the following teaching from Ansel's: "certain drugs are chemically unstable in solution but stable when suspended. . . . [T]he suspension ensures chemical stability while permitting liquid therapy." (JTX-17 at 70.) Actavis further points to Dr. Jacobs', Tris's expert, admission that a POSA would have known that ion exchange resin technology was a means of making a stable liquid suspension. (Tr. 953:18-954:2 (Jacobs).)

In addition to the foregoing, Actavis relies on both the Ansel's and Connors prior art references to support its position that MPH at the claimed pH would have been obvious. Actavis asserts that Ansel's teaches the use of ion exchange resin technology to make extended-release liquid formulations. (JTX-17 at 6, 59-60.) Actavis further contends that Ansel's discloses that by using a mixture of coated and uncoated beads, release can be extended over 12 hours. (JTX-17 at 60.) Actavis further argues that Ansel's teaches specific methods of stabilizing drugs that, like methylphenidate, are subject to hydrolysis. (D.I. 152 at 14.) Those methods include three that appear as limitations in the asserted claims: use of a suspension; optimization of pH; and formulation as dry powder for reconstitution. (JTX-17 at 25.)

Actavis notes that Ansel's teaches that "pH is a major determinant of the stability of a drug prone to" hydrolysis. (JTX-17 at 25.) The Connors reference disclosed that the pH of optimal stability for methylphenidate in an aqueous solution is 3.5. (D.I. 152 at 2, 19.) Actavis argues that this is indisputably within the claimed pH range of about 3.5 to about 5. (JTX-24 at 3; Tr. 453:1-10, 540:22-541:11) Under Federal Circuit law, since the prior art pH values overlap with the claimed pH range, the claimed pH range is *prima facie* obvious. *See Iron Grip Barbel Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1321-22 (Fed. Cir. 2004); *In re Peterson*, 315 F.3d at 1329 ("A *prima facie* case of obviousness typically exists when the ranges of a claimed composition overlap

the ranges disclosed in the prior art. . . . [E]ven a slight overlap in range establishes a *prima facie* case of obviousness.")

In contrast, Tris contends that Actavis' experts provided no evidence of motivation or reasonable expectation that a POSA would have successfully designed a product with the first two combinations (relating to formulation) in the '033 patent claim 10: (1) an aqueous MPH liquid product[5] and (2) with a pH of about 4 to about 4.5.[6] (D.I. 151 at 29.) Tris discusses three prior art references in support of its conclusion that MPH aqueous liquid would not have been obvious: (1) Connors; (2) Herman; and (3) Ansel's. According to Tris, Connors taught that MPH "undergoes typical ester hydrolysis in aqueous solutions." (JTX-24 at 2.) The Herman reference used organic (non-aqueous) solvents and confirmed that MPH is unstable in water, specifically teaching "methylphenidate HCl has not been chemically stable in conventional liquid vehicles" and [a] completely ***aqueous solvent system is not suitable for a methylphenidate HCl solution*** due to problems with solubility and stability." (JTX-33 at 1:25-26, 2:16-18; Tr. 883:6-24 (Jacobs).) Furthermore, Tris maintains that Ansel's taught to reduce or eliminate water for a drug that undergoes hydrolysis. (JTX-17 at 25; Tr. 881:9-25 (Jacobs).) Tris contends that Ansel's proposed using liquids other than water, such as glycerin and propylene glycol. (*Id.*) With respect to pH, Tris contends that the inventors discovered a pH range where the formulation of the asserted claims has improved stability, resulting in unexpected results over the prior art disclosure of a pH of "about" 3.5 and below. (D.I. 151 at 30-31.) Tris relies on Dr. Jacob's testimony which explained that, given the many variables involved in formulating a product, a POSA would have relied on

[5] The court notes that this component is also in all asserted '033, '390, and '649 patent claims; the '765 patent claims 6, 13, 16, 18, 20, and 30 (aqueous MPH suspension); and '765 patent claim 25 and all '083 patent claims (powder for reconstitution with water).

[6] The court notes that this component is also in the '765 patent claim 20 (about 4 to about 4.5); '649 patent claim 22 and all '083 patent claims (about 4.2); '649 patent claims 26, 33 (3.5 to 5); '765 patent claims 6, 13, 16, 18, 25, 30, and d'033 patent claim 4 (about 3.5 to about 5).

the pH of maximum stability in the literature and not performed unnecessary experiments. (Tr. 957:14-958:13 (Jacobs).)

Despite Tris' arguments, for several reasons, the court is persuaded that there was a motivation to combine the teachings of the prior art references to achieve the MPH formulation, and that the skilled artisan would have had a reasonable expectation of success in doing so. The court concludes that Dr. Moreton's opinion provides sound reasoning that supports his determination that the asserted claims regarding MPH formulation are invalid for obviousness.[7] While Tris' expert, Dr. Jacobs, testified that Mehta disclosed the use of "numerous active ingredients," there is no dispute that Mehta provides a specific example of how to prepare ion exchange resins using methylphenidate, and contains claims directed to methylphenidate formulations. (JTX-40 at 13 (Example 4); Tr. 488:9-21 (Moreton); Tr. 940:11-942:8 (Jacobs).) Dr. Moreton's testimony does not suggest that Mehta, alone, solves the instability problem with regard to MPH in water, but Actavis adduced credible evidence that a POSA would have also looked to Ansel's for guidance.

The court recognizes that Dr. Moreton did not refute Herman, the MPH-specific prior art, that expressly teaches MPH is unstable in water. (D.I. 151 at 29.) Nonetheless, a POSA would not have ignored the express teachings in Ansel's that taught how to make stable aqueous formulations with a drug like methylphenidate that is subject to hydrolysis. If "there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR,* 550 U.S. at 421. The record demonstrates that making suspensions, formulated as a dry powder for reconstitution and

[7] In an attempt to undermine the credibility of Dr. Moreton, Tris points out his lack of experience with an extended release suspension, ion exchange resins, and MPH. (D.I. 151 at 32.) The court is not persuaded for two reasons: first, the court has accepted Dr. Moreton as a POSA and, second, his opinions are supported by the prior art.

optimizing pH, represented three of the five methods to avoid hydrolysis disclosed in the prior art. (D.I. 152 at 22.) Unlike *Dey, L.P. v. Teva Parenteral Medicines, Inc.*, 6 F. Supp. 3d 651, 677 (N.D.W. Va. 2014) where there was no evidence "that any combination of the prior art would indicate that an aqueous formulation of [the active ingredient] with long-term stability was possible," here, the prior art suggests specific methods to overcome the stability problem in creating an MPH formulation.

The court agrees, as Actavis argues, that the disclosure in the prior art of overlapping pH ranges would have provided sufficient motivation to optimize the pH, and it was not inventive to do so. (D.I. 152 at 20.) "[T]he existence of overlapping or encompassing ranges shifts the burden to the applicant to show that his invention would not have been obvious." *In re Peterson*, 315 F.3d at 1330. In order to meet its burden, the patentee must establish "'that the [claimed] range is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range.'" *In re Peterson*, 315 F.3d at 1330 (quoting *In re Geisler*, 116 F.3d 1465, 1469-70 (Fed. Cir. 1997)). The showing of unexpected results "must be commensurate in scope with the claimed range." *Id.* Although it had the burden to do so, Tris submitted no particularized evidence demonstrating that the scope of the claimed pH range exhibits unexpected results over the prior art disclosure of a pH of "about" 3.5. (D.I. 152 at 20.) In fact, Dr. Jacobs admitted that the Connors reference tells formulators to "adjust their formulation to that pH," and that "there's a higher likelihood of success if you used that 3.5." (Tr. 884:20- 885:16. (Jacobs).)

Moreover, the asserted claims that have a narrower pH range of "about 4 to about 4.5", despite being outside the prior art disclosures, are not nonobvious. Applying the court's construction of "about," however, "about 4" literally encompasses pH values as low as 3.6. Where a claimed range abuts a prior art range, the claimed range is also *prima facie* obvious. *In re*

Peterson, 315 F.3d at 1329; *see also In Re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990) (finding claimed range obvious where the prior art range abutted the claim range). As with the pH range of 3.5 to 5, Tris cannot overcome the presumption that the narrower claimed pH range of 4 to 4.5 is obvious because it cannot meet its burden of showing that that specific range is critical. The patents-in-suit make clear that "the product is most stable at pH between 3.5 and 5.0." (JTX1 at 25.) Mr. Mehta and Dr. Jacobs both admitted that the claimed formulation is stable across the full pH range of 3.5 to 5. (Tr. 116:19-117:4 (Mehta); 968:22-969:9, 970:15-971:9, 971:20-24 (Jacobs).) Thus, there is nothing critical about the narrower range of 4 to 4.5. *See, e.g., Warner Chilcott Co. v. Teva Pharmaceuticals USA, Inc.*, 89 F. Supp.3d 641, 655-56 (D.N.J. 2015) (Hochberg, J.), *aff'd,* 642 F. App'x 996 (Fed. Cir. 2016) (claimed amount of excipient found not critical where specification of patent disclosed that amounts of excipient outside the claimed amount were also effective).

In sum, the court is not convinced that the asserted claims include pH range limitations that are critical to the claimed suspension's stability. (D.I. 151 at 10.) Accordingly, the court concludes that Actavis has shown by clear and convincing evidence that a POSA would have been motivated to ***and*** have had a reasonable expectation of success combining MPH with water, at the claimed pH, in an ion-exchange resin to achieve the claimed liquid MPH product.

b. Pharmacokinetic Features & Clinical Effects: Achieving 45 minute onset and 12 hour effect despite MPH's short half-life

The court considers whether it would have been obvious to obtain the pharmacokinetic features and clinical effects of Quillivant XR®. Actavis contends that, despite the number of peaks being of little relevance to a POSA, the prior art disclosed Single Peak profiles with early onset of action and long duration of effect. (D.I. 152 at 24.) Specifically, Actavis characterizes the Scicinski reference, Daytrana, Concerta, and Metadate CD profiles as Single Peak. (*Id.*) Actavis

argues that the plasma profiles of the prior art extended methylphenidate products Daytrana, Concerta, and Metadate CD as well as the Scicinski reference target profile would have suggested to a POSA that a Single Peak profile could provide early onset of action and extended duration of effect.

In response, Tris contends that the claimed PK features and clinical effects were not obvious. Specifically, Tris asserts that Actavis did not show why a POSA would have a reasonable expectation of success, be motivated, or have a reason to design a product with the clinical and PK features in '033 patent claim 10, namely: (1) a single mean peak profile to achieve a 45 minute onset and 12 hour effect with oral MPH (also in '765 patent claim 20); (2) an early T_{max} of about 4 to about 5.25 hours, to achieve a 12 hour effect with oral MPH (also in '765 patent claim 20); or (3) the claimed ranges for T_{max} and $T_{1/2}$ (also in '765 patent claims 6, 13, 16, 18, 20 & 30, '033 patent claim 4, and '390 patent claims 15, 16, & 20).

Both at trial and in their post-trial briefings, the parties' obviousness arguments focus on whether the 2nd generation MPH products illustrate single or bimodal peak profiles. As a preliminary matter, there is no dispute that Daytrana has a Single Peak plasma profile. (JTX-79 at 10-11; Tr. 290:11-291:10 (Staller); Tr. 758:23-759:10 (McGough).) Actavis' expert, Dr. Staller, testified that Concerta's plasma profile has also been described in some prior art references as having a Single Peak. Dr. Staller observed that the PDR entry for Concerta lists its plasma profile as having a single C_{max} and a single T_{max}, which would have indicated to a POSA that it has a Single Peak. (Tr. 291:11-293:7 (Staller).) Similarly, Dr. Staller explained that the plasma profile for Metadate CD that appears in the Gonzalez reference has a Single Peak. (JTX-32 at 6 Figure 2(a); Tr. 294:14-296:4 (Staller).)

In contrast, Tris argues that, after the failure of Ritalin-SR®, the second generation of extended release solid oral MPH product—Concerta®, Metadate CD®, Ritalin® LA, and Focalin®—were developed using two components, IR and ER, to provide two peak (bimodal) profiles. (Tr. 851:25-855:8, 867:19-868:4 (Jacobs); Tr. 686:17-687:4 (McGough).) In support of its argument, Tris cites Drs. Staller and McGough's testimony, which indicated the failure of Ritalin-SR® to achieve the desired sustained effect. (D.I. 151 at 12.) Dr. McGough explained that the prior art showed that "acute tolerance"[8] or "tachyphylaxis" was one of the reasons for the deficiency of Ritalin-SR®. (Tr. 676:24-680:2, 682:12-685:11, 685:24-693:24 (McGough); JTX-47 at 6; JTX-66 at 2; PTX-215 at 3.) Actavis' expert, Dr. Staller, agreed that "some of the experts in the prior art were arguing about . . . tachyphylaxis or other problems and they were arguing against or away from a single peak." (Tr. 353:18-20 (Staller).)

Tris also contends that the state of the art second generation oral MPH products used bimodal profiles and delayed T_{max} to extend effect. (D.I. 151 at 13.) In support of this position, Tris adduced evidence illustrating that second generation products were designed to mimic the peaks and valleys of multiple IR dosing. (Tr. 674:7-8, 675:13-18, 692:20-693:25, 705:6-13, 687:11, 722:13-723:7, 769:10-24, 771:9-14 (McGough); JTX-66 at 2; JTX-47 at 6.) The Gonzalez reference disclosed: "[Concerta®] . . . exhibited biphasic characteristics . . . consisting of a sharp initial increase followed by a second increase in MPH plasma levels—resulting in two peak plasma concentrations (C_{max}-1 and C_{max}-2)." (JTX-32 at 5; Tr. 703:18-704:13 (McGough; Tr. 228:16-230:6 (DeVane).) Tris also notes that Concerta achieves a 12 hour effect with a late T_{max} but does not achieve a 45 minute onset. (Tr. 704:14-705:5, 735:2-5, 735:21-736:6 (McGough); JTX-23 at

[8] Acute tolerance is the theory that as the day progress, higher blood levels are required to produce the same therapeutic effects. (Tr. 677:12-678:10 (McGough).)

5-6.) Tris further points out that Actavis' expert, Dr. Straughn, agreed that the Tmax for Concerta is later than the claimed range in the patents-in-suit. (Tr. 404:6-15, 394:15-23 (Straughn).)

Similarly, Gonzalez explains the first peak/shoulder of the Metadate CD® curve was understood to be a peak because it is followed by a second increasing phase: "[Metadate CD ®] . . . exhibited biphasic characteristics . . . consisting of a sharp initial increase followed by a second increase in MPH plasma levels—resulting in two peak plasma concentrations (Cmax-1 and Cmax-2)." (JTX-32 at 5; Tr. 706:10-17 (McGough).) Tris argues that Metadate CD has an earlier T_{max} than Concerta (4.4-5 hours) but also has a significantly shorter duration of action of 6-8, not 12, hours. (Tr. 876:9-17, 877:12-15 (Jacobs); JTX-79 at 7, 24; JTX-38 at 7; Tr. 667:11-12 (McGough); Tr. 276:15-19 (Staller).)

Tris' and Actavis' experts agreed that Ritalin® LA's and Focalin® XR's profiles have two peaks. (Tr. 707:14-708:15, 708:17-709:2 (McGough); Tr. 321:8-11, Tr. 321:24-25 (Staller); JTX-48 at 3, JTX-31 at 4, 5.) Tris provided evidence to show that Ritalin LA has a relatively early T_{max} (5.5 hours) and achieves only 6-8 hours of effect. (Tr. 877:16-878:16 (Jacobs); JTX-48 at 3; Tr. 398:4-399:10 (Straughn).) Tris argues that the prior art taught the following: (1) the failure of the single mean peak Ritalin-SR® product and the relative success of the two peak second generation products at extending effect for MPH taught or led away from using a single mean peak profile to achieve 45 minute onset and 12 hour effect; and (2) the art taught or led away from using an early T_{max} to provide 12 hours of effect. (D.I. 151 at 17.) Given the prior art, Tris contends that it would have been unexpected that Tris' invention was able to provide 12 hour effect with an early T_{max}. (Tr. 761:2-18, 762:6-8, 795:10-11 (McGough).) While the court believes Tris' evidence regarding the second generation products is persuasive, it is not dispositive on the obviousness inquiry.

Importantly, the Scicinski reference describes the purpose of its invention as providing an oral dosage form of methylphenidate that has a long duration of action and rapid onset. (JTX-50 at 23-24 ¶ 61.) A POSA would have undoubtedly considered Scicinski because its purpose aligns with what the parties agreed that a POSA would have been motivated to do in the present case. (D.I. 141 ¶ 137; Tr. 284:4-17 (Staller).) Actavis' expert, Dr. Staller, testified that Scicinski Figure 7 discloses a target plasma profile for his methylphenidate product that has a Single Peak and a 12-hour duration of action. (JTX-50 at 7, Figure 7; Tr. 284:18-285:6 (Staller).) In the text of the application, Scicinksi provides a description of what the target plasma profile looks like. (D.I. 152 at 15; Tr. 285:7-286:10 (Staller).) While Dr. McGough testified that a Single Peak profile would have been nonobvious, he did not testify that there was any benefit to having a profile with one peak instead of two. (D.I. 152 at 24.)

To counter, Tris' experts testified that the target profile in Scicinski is bimodal based on a contention that Figure 7 is a "blend" of the Metadate CD and Concerta plasma profiles. (D.I. 151 at 18.) This theory is flawed, however, because both Drs. McGough and Jacobs conceded that Scicinski does not expressly claim to be targeting a blend of products. (Tr. 786:20-787:6 (McGough); Tr. 986:4-7 (Jacobs).) Instead, Scicinski describes the target profile as "improved" and "novel and unique." (JTX-50 at 23; Tr. 787:15-788:7 (McGough).) In order to undermine the weight of Scicinski, Tris further argues that Scicinski's product is "hypothetical." In other words, the product was never made and there is no data to support that the target profile could be achieved. Actavis' expert, Dr. Straughn, testified, however, that POSAs would have used the well-known technique of deconvolution to achieve a product that meets a target pharmacokinetic profile like that in Scicinski Figure 7. (Tr. 383:3-383:3 (Straughn).) As Tris failed to adduce any compelling

evidence to persuade the court to discount prior art simply because it contains a prophetic example, the court finds that Scicinski teaches toward a Single Peak.

Furthermore, Actavis provided evidence concerning the pharmacokinetic details of the second generation products. First, Actavis notes that the AUCs for Concerta and Ritalin LA, when normalized to a 60 mg dose as in the Asserted Claims, are 139.3 ng-hr/ml and 137.4 ng-hr/ml, respectively. (Tr. 372:7-20 (Straughn).) Dr. Straughn testified that these values fall within the claimed AUC range (which, factoring in the construction of "about," is 102.6-198 ng-hr/ml). (DTX-206 at 4-6; Tr. 371:9-15, 373:3-5 (Straughn).)[9] Second, according to Dr. Straughn, the C_{max} values for a 60 mg dose of Concerta would be 12.3 ng/ml, and for Rtialin LA would be 15.9 ng/ml and 18.6 ng/ml (Ritalin LA has two C_{max}'s). (Tr. 369:10-25, 372:7-16, 373:7-16 (Straughn).) These values fall within the claimed C_{max} range (which, factoring in the construction of "about," is 9.9-18.7 ng/mL). (DTX-206 at 4-6; Tr. 373:7-19, 374:7-18, 375:6-8 (Straughn).) Lastly, Dr. Straughn explained that a POSA would not have targeted a specific T_{max} or half-life, because those parameters do not control the onset or duration of effect. (Tr. 380:18-25, 377:3-17 (Straughn).) Rather, Actavis contends that a POSA would have expected the T_{max} and half-life to be similar to that of the existing extended-release methylphenidate products, which had T_{max} ranging from 4.4 and 8 hours and half-life ranging from 3.3 to 6.8 hours. (Tr. 364:12-24, 378:19-380:17, 381:2-19, 381:24-382:2 (Straughn); JTX-38 at 7-8.) Actavis contends that these expected ranges overlap with the claimed ranges, which for T_{max} is 3.6-5.78 hours and for half-life is 4.5-7.7 hours (factoring in the construction of "about" for both). (DTX-206 at 4-6; Tr. 381:2-23 (Straughn).)

[9] Given the undisputed fact that methylphenidate HCl exhibits dose-proportionality and therefore linear pharmacokinetics, AUC and C_{max} values for both Concerta (18 mg) and Ritalin LA (20 mg) can be normalized to an equivalent 60 mg dose by multiplying each value by the appropriate ratio. (Tr. 371:23-372:20, 373:7-16 (Straughn).)

Finally, although Tris' expert, Dr. McGough, testified that a POSA would not have expected a formulation with a single peak to achieve both early onset and extended duration of action, he admitted that he would "defer completely to a formulator in terms of what sort of curve could be achieved." (Tr. 794:9-19, 795:15-23 (McGough).) As a result, the court finds the testimony of Actavis' formulator is more compelling. Accepting as credible Dr. Moreton's testimony that a formulator would have had no trouble achieving early onset of action and extended duration of effect with a Single Peak profile as of the priority date.,(Tr. 507:25-509:10 (Moreton)), the court finds Tris' arguments unpersuasive. Tris' nonobvious argument hinges primarily on the plasma profile and fails to sufficiently weigh the pharmacokinetic details that would have been known to skilled artisans or the prior art teachings that disclosed how to optimize an MPH product.[10]

Actavis asserts, that a POSA would have routinely optimized the ratio of IR to ER components. (D.I. 152 at 28.) This assertion is notable. First, Mehta taught that ion exchange resin formulations could contain "any suitable ratio" of uncoated and coated ion exchange complexes. (JTX-40 at 9; Tr. 490-25:491:20 (Moreton).) As Dr. Moreton explained, and Dr. Jacobs agreed, the uncoated complexes provide immediate release of the drug, while the coated complexes provide extended release. (Tr. 491:8-16, 496:2-8 (Moreton); Tr. 945:3-13 (Jacobs).) Actavis argues a POSA would have understood that a formulation incorporating both an uncoated immediate release portion and a coated sustained release portion would be a way to achieve the target formulation in this case. (D.I. 152 at 28.) The court agrees.

[10] The court acknowledges that the inventors themselves testified that they were not concerned with the number of peaks in Qullivant's plasma profile. In fact, Mr. Mehta testified, "when we were developing, our goal was really to have faster and rapid onset of action and a long duration." (Tr. 72:17-22 (Mehta).) Dr. Tu similarly testified that when he started the project there was no pharmacokinetic profile he was trying to achieve, and he did not set out to avoid a bimodal release profile. (Tr. 431:17-23 (Tu).)

In addition to Mehta, Dr. Moreton testified that a POSA would have looked to commercially available formulations as a starting point to determine an appropriate ratio. (Tr. 501:3-11 (Moreton).) As of July 10, 2010, there were four commercially available two-component methylphenidate formulations: Concerta, Metadate CD, Ritalin LA, and Focalin XR. *See* Tr. 500:23-503-5 (Moreton). As noted above, it is undisputed that Concerta and Metadate CD contained an immediate release component and a sustained release[11] component in 22:78 and 30:70 rations, respectively. (D.I. 141 ¶ 165, 169.) It is also undisputed that Ritalin LA and Focalin XR contained an immediate release component and a delayed release[12] component, both in 50:50 ratios. (*Id.* ¶ 171, 175.) According to Actavis, a POSA would have focused on the ratios of Concerta and Metadate CD, which had plasma profiles close to the desired target. (D.I. 152 at 29.) Dr. Moreton explained that a POSA would have tested a ratio at or near those prior art ratios and optimized the formulation to achieve the desired profile. *See* Tr. 507:25-508:10, 508:14-20 (Moreton).)

Tris' expert, Dr. Jacobs, claimed that Dr. Moreton ignored Ritalin LA and Focalin XR as a result of hindsight bias. (Tr. 951:10-952:20 (Jacobs).) To the contrary, this does not appear to be a case of Monday-morning quarterbacking. Dr. Moreton credibly explained that a POSA would have declined to use the 50:50 ratios in those products because they resulted in a two-peak plasma profile having the peaks and valleys that a POSA would have wanted to avoid. (Tr. 504:2-10 (Moreton).) The asserted claims are directed to ratios of about 10:90 to about 30:30, *see* DTX-206, which overlap with the prior art Concerta and Metadate CD ratios.[13] This further supports

[11] "Sustained release" in this context refers to a component that begins release upon administration, but that has a slow release of drug over time. (Tr. 501:25-502:5 (Moreton).)

[12] "Delayed release" in this context refers to a component that does not release any drug until a specified time or location in the gastrointestinal tract. Once that time has passed or location is reached, the delayed release component releases all of its drug, as if it were an immediate release component. (Tr. 502:11-18 (Moreton).)

[13] The court finds that even the narrowest claimed ratio of "about 20%" immediate release overlaps with the Concerta ratio, given the 10% variance in the term "about." *See* DTX-206 at 14; D.I. 78 at 4.

the conclusion that the asserted claims are *prima facie* obvious. *See Iron Grip*, 392 F.3d at 1321-22.

For the reasons stated above, the court concludes that a POSA in 2010 would have had a reasonable expectation of success that, by combining the teachings and disclosures known in the prior art, the claimed liquid MPH product was possible.

(4) Secondary Considerations

Once a *prima facie* case of obviousness has been established, the burden then shifts to the applicant to present evidence of secondary considerations of nonobviousness to overcome the *prima facie* showing. *See, e.g., In re Huang*, 100 F.3d 135, 139 (Fed.Cir.1996). The Supreme Court has made clear that secondary considerations can include, among other things, evidence of commercial success, long-felt but unsolved needs, and/or the failure of others. *See Graham*, 383 U.S. at 17–18, 86 S.Ct. 684. A plaintiff may also rebut an obviousness contention by demonstrating that there were unexpected results created by the claimed invention, unexpected properties of the claimed invention, licenses showing industry respect for the invention, and/or skepticism of skilled artisans before the invention. *See In re Rouffet*, 149 F.3d 1350, 1355 (Fed.Cir.1998).

"Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion." *Pfizer*, 480 F.3d at 1372. Moreover, "[a] nexus between the merits of the claimed invention and evidence of secondary considerations is required in order for the evidence to be given substantial weight in an obviousness decision." *Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1327 (Fed.Cir.2008) (alteration in original) (quoting *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 668 (Fed.Cir.2000)). In other words, the secondary considerations, must be commensurate in scope—"coextensive"—with the claimed features of the invention. *Id.*;

see also MeadWestVaco Corp. v. Rexam Beauty & Closures, Inc., 731 F.3d 1258, 1264–65 (Fed.Cir.2013).

Here, Tris argues that, even should the court determine that Actavis established a *prima facie* case on the issue of obviousness, the secondary consideration of unexpected properties, long-felt but unmet need, commercial success, and copying effectively rebut the showing. (D.I. 151 at 39.); *see Ortho-McNeil Pharm., Inc. v. Mylan Labs, Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008). The court will address each secondary consideration in turn.

i. Unexpected Properties

Unexpected results may be demonstrated by showing "that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed.Cir.2009). This comparison is made to the closest prior art. *Kao Corp v. Unilever U.S. Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006). Tris adduced evidence that its invention unexpectedly provided: (1) stability for MPH in water; (2) optimal stability at a pH of about 4.2 and about 4 to about 4.5; (3) both a 45 minute onset and 12 hour effect with a single mean peak profile; (4) a 12 hour effect with an early T_{max} of about 4 to about 5.25 hours; and (5) more rapid and complete absorption when taken with food compared with the fasted state. (D.I. 151 at 24.) Neither Dr. Jacobs nor Dr. McGough offered an opinion comparing the claimed invention to the closest prior art. In fact, Dr. Jacobs testified that he had no opinion as to what the closest prior art is. (Tr. 973:16-973:5 (Jacobs).) Absent the proper comparison to the closest prior art, their opinions are, as a matter of law, irrelevant to the issue of unexpected results.

Even if the court considers Tris' arguments, the evidence on the record militates against a finding that the claimed MPH liquid formulation exhibited unexpected properties. Particularly,

Actavis established that the claimed pH range overlaps with the pH values identified in the prior art as being most stable. (JTX-24 at 2; Tr. 453:1-10 (Moreton).) The record evinces no dispute that Ansel's taught a POSA how to make stable aqueous formulations with drugs like methylphenidate in aqueous formulations, including optimizing pH. (Tr. 462:12-463:3 (Moreton); Tr. 936:4-18, 937:9-12, 952:21-954:2, 992:18-993:11 (Jacobs).)

With respect to the claimed Single Peak limitation, the prior art Scicinski reference, the Daytrana, Concerta, and Metadate CD products would have provided the expectation that a Single Peak plasma profile could provide for rapid onset and extended duration of action. (Tr. 283:14-21, 290:4-10 (Staller).) As to the purported "beneficial food effect" when taken with food, first the Quillivant label itself provides pharmacokinetic information on the effect of food, and reveals that Quillivant has "no clinically relevant food effect." (DTX-33 at 13; Tr. 749:16-750:20 (McGough).) Second, while Dr. McGough testified at trial that Quillivant has a "beneficial food effect," he stated the exact opposite in his expert report: "Quillivant demonstrates a lack of any clinically significant food effect." (Tr. 748:6-749:15 (McGough).) Third, Dr. McGough testified that he has not prescribed Quillivant because of this purported "beneficial food effect." (Tr. 750:17-20 (McGough).) The court therefore concludes that there is no credible evidence of unexpected properties to overcome a finding of obviousness.

ii. Long-felt Need

The court finds that the evidence on the record does the support a finding that the claimed MPH product serves a long felt but unmet need. Although methylphenidate was first used in 1955, the mere passage of time is insufficient to establish a long felt need. *See In re* Kahn, 441 F.3d 977, 990-91 (Fed. Cir. 2006) ("This is because '[a]bsent a showing of long-felt need or the failure of others, the mere passage of time without the claimed invention is not evidence of

nonobviousness.'" (citing *Iron Grip Barbell Co.*, 392 F.3d at 1325)). The evidence Tris presented at trial is also unavailing. Dr. McGough's expert report, where he stated that Metadate CD, Ritalin LA, and Concerta had already achieved the goal of once daily dosing, undermines his contention that Quillivant was the first to achieve effective once daily dosing. (Tr. 734:9-17 (McGough).) In addition, the prior art disclosed, and Dr. McGough conceded, that the second generation products have onset of action in as early as 30 minutes. (JTX-19 at 2; Tr. 741:22-742:6 (McGough).) Dr. McGough further testified that there was a long-felt need for a drug for children who had trouble swallowing based on the "significant drawbacks" of the patch product Daytrana. (Tr. 776:5-7 (McGough).) This contention is undermined by Dr. McGough's own writings where in the book he authored entitled "ADHD," the doctor writes that Daytrana is a product that is "particularly useful when swallowing is difficult." (PTX-286A at 86; Tr. 776:18-777:18 (McGough).)

iii. Commercial Success

Tris claims that Quillivant is a commercial success. Company founder and CEO Ketan Mehta testified the product totaled $180 million in sales and 600,000 prescriptions in 2016. (Tr. 86:23-87:10 (Mehta).) Mehta testified that Pfizer purchased NextWave (the company to whom Tris licensed the product) for $290 million and potential additional milestone payments. (Tr. 86:13-17 (Mehta).) He also testified that the price was attributable to Qullivant XR® because it was the only approved product at the time. (Tr. 86:19-22 (Mehta).) Commercial success is only relevant to the nonobvious inquiry if there is a nexus between the success and the asserted claims of the patent-in-suit. Even if this constitutes some evidence of nexus, "evidence related solely to the number of units sold," which Mr. Mehta provided, constitutes a "very weak showing of commercial success." *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996). "[T]he more probative evidence of commercial success relates to whether the sales represent a substantial quantity in the

market." *In re Applied Materials, Inc.*, 692 F.3d 1289, 1300 (Fed. Cir. 2012) (internal quotations omitted). Tris has provided at best evidence of a modest level of commercial success for Quillivant.

iv. Copying

Tris established that Actavis's documents acknowledge that Actavis copied claimed formulation features not required to be identical for FDA approval, including excipients and pH. (D.I. 151 at 25; Tr. 928:15-19 (Jacobs).) "A showing of copying is only equivocal evidence of nonobviousness in the absence of more compelling objective indicia of other secondary considerations." *Ecolochem, Inc. v. S. California Edison Co.*, 227 F.3d 1361, 1380 (Fed. Cir. 2000). Further, "demonstration that a defendant has copied a patented invention is not compelling evidence of nonobviousness in the Hatch–Waxman context due to the unique nature of the ANDA process." *Allergan, Inc. v. Watson Labs., Inc.–Florida*, 869 F.Supp.2d 456, 485 (D. Del. 2012). Therefore, the court does not find copying to be strong objective evidence of nonobviousness in this case. Tris has failed to rebut Actavis's *prima facie* case of obviousness.

IV. CONCLUSION

For the reasons stated above, the court concludes that the asserted claims of the patent-in-suit are invalid as obvious under 35 U.S.C. § 103.

Dated: September 5, 2017

UNITED STATES DISTRICT JUDGE